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(12) (19) (CA) **Demande-Application**

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(54) **DERIVES PEPTIDIQUES ANTIVIRAUX**
(54) **ANTIVIRAL PEPTIDE DERIVATIVES**

B1063
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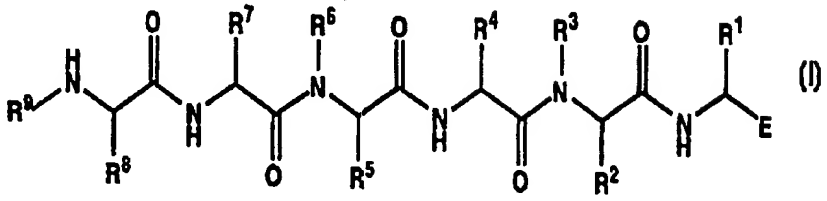
prior art



(I)

(57) L'invention concerne des dérivés d'acides aminés de la formule (I) et des sels de composés acides de ladite formule (I) ayant des bases qui, en tant qu'inhibiteurs de la protéinase virale, sont utiles comme agents antiviraux, en particulier pour le traitement ou la prophylaxie d'infections causées par l'hépatite C, l'hépatite G ou des virus GB humains. Dans ladite formule (I), E représente CHO ou $B(OH)_2$; R_1 représente alkyle inférieur (éventuellement substitué par halo, cyano, alkylthio inférieur, aryl-alkylthio inférieur, aryle ou hétéroaryle), alcényle inférieur ou alkynyle inférieur; R^2 représente alkyle inférieur éventuellement substitué par hydroxy, carboxy, aryle, aminocarbonyle ou cycloalkyle inférieur; et R^3 représente hydrogène ou alkyle inférieur; ou R^2 et R^3 représentent ensemble un di- ou un triméthylène éventuellement substitué par hydroxy; R^4 représente alkyle inférieur (éventuellement substitué par hydroxy, cycloalkyle inférieur, carboxy, aryle, alkylthio inférieur, cyano-alkylthio inférieur ou aryl-alkylthio inférieur), alcényle inférieur, aryle ou cycloalkyle inférieur; R^5 représente alkyle inférieur (éventuellement substitué par hydroxy, alkylthio inférieur, aryle, aryl-alkylthio inférieur ou cyano-alkylthio inférieur) ou cycloalkyle

(57) The invention provides amino acid derivatives of formula (I) wherein E represents CHO or $B(OH)_2$; R^1 represents lower alkyl (optionally substituted by halo, cyano, lower alkylthio, aryl-lower alkylthio, aryl or heteroaryl), lower alkenyl or lower alkynyl; R^2 represents lower alkyl optionally substituted by hydroxy, carboxy, aryl, aminocarbonyl or lower cycloalkyl; and R^3 represents hydrogen or lower alkyl; or R^2 and R^3 together represent di- or trimethylene optionally substituted by hydroxy; R^4 represents lower alkyl (optionally substituted by hydroxy, lower cycloalkyl, carboxy, aryl, lower alkylthio, cyano-lower alkylthio or aryl-lower alkylthio), lower alkenyl, aryl or lower cycloalkyl; R^5 represents lower alkyl (optionally substituted by hydroxy, lower alkylthio, aryl, aryl-lower alkylthio or cyano-lower alkylthio) or lower cycloalkyl; R^6 represents hydrogen or lower alkyl; R^7 represents lower alkyl (optionally substituted by hydroxy, carboxy, aryl or lower cycloalkyl) or lower cycloalkyl; R^8 represents lower alkyl optionally substituted by hydroxy, carboxy or aryl; and R^9 represents lower alkylcarbonyl, carboxy-lower alkylcarbonyl, arylcarbonyl, lower

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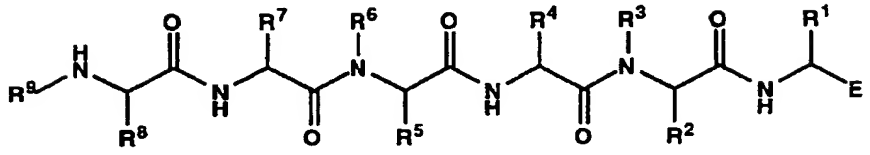
inférieur; R^6 représente hydrogène ou alkyle inférieur; R^7 représente alkyle inférieur (éventuellement substitué par hydroxy, carboxy, aryle ou cycloalkyle inférieur) ou cycloalkyle inférieur; R^8 représente alkyle inférieur éventuellement substitué par hydroxy, carboxy ou aryle; et R^9 représente alkylcarbonyle inférieur, carboxy-alkylcarbonyle inférieur, alkylcarbonyle, alkylsulfonyle inférieur, arylsulfonyle, alcoxycarbonyle inférieur ou aryl-alcoxycarbonyle inférieur.

alkylsulphonyl, arylsulphonyl, lower alkoxycarbonyl or aryl-lower alkoxycarbonyl, and salts of acidic compounds of formula (I) with bases, which are viral proteinase inhibitors useful as antiviral agents, especially for the treatment or prophylaxis of infections caused by Hepatitis C, Hepatitis G and human GB viruses.

Claims

1. Compounds of the general formula



(I)

wherein

E represents CHO or $B(OH)_2$;

R^1 represents lower alkyl, halo-lower alkyl, cyano-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, aryl-lower alkyl, heteroaryl-lower alkyl, lower alkenyl or lower alkynyl;

R^2 represents lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, aminocarbonyl-lower alkyl or lower cycloalkyl-lower alkyl; and

R^3 represents hydrogen or lower alkyl; or

R^2 and R^3 together represent di- or trimethylene optionally substituted by hydroxy;

R^4 represents lower alkyl, hydroxy-lower alkyl, lower cycloalkyl-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, lower alkenyl, aryl or lower cycloalkyl;

R^5 represents lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkyl, aryl-lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl or lower cycloalkyl;

R^6 represents hydrogen or lower alkyl;

R^7 represent lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, lower cycloalkyl-lower alkyl or lower cycloalkyl;

R^8 represents lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl or aryl-lower alkyl; and

R^9 represents lower alkylcarbonyl, carboxy-lower alkylcarbonyl, arylcarbonyl, lower alkylsulphonyl, arylsulphonyl, lower alkoxycarbonyl or aryl-lower

alkoxycarbonyl,
and salts of acidic compounds of formula I with bases.

2. Compounds of the general formula I according to claim 1.

3. Compounds according to claim 1, wherein R^1 represents lower alkyl, halo-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, heteroaryl-lower alkyl, lower alkenyl or lower alkynyl.

4. Compounds according to claim 3, wherein the halo-lower alkyl group is fluoro-lower alkyl.

5. Compounds according to claim 3, wherein the hetero-aryl-lower alkyl group is thienyl-lower alkyl or furyl-lower alkyl.

6. Compounds according to any one of claims 1 to 5, wherein R^2 represents lower alkyl, lower cycloalkyl-lower alkyl or aryl-lower alkyl.

7. Compounds according to any one of claims 1 to 6, wherein R^3 represents hydrogen.

8. Compounds according to any one of claims 1 to 5, wherein R^2 and R^3 together represent trimethylene optionally substituted by hydroxy.

9. Compounds according to any one of claims 1 to 8, wherein R^4 represents lower alkyl, lower cycloalkyl-lower alkyl, aryl-lower alkyl, aryl or lower cycloalkyl.

10. Compounds according to any one of claims 1 to 9, wherein R^5 represents aryl-lower alkyl or lower cycloalkyl.

11. Compounds according to any one of claims 1 to 10, wherein R^6 represents hydrogen.

12. Compounds according to any one of claims 1 to 11, wherein R^7 represents lower alkyl, carboxy-lower alkyl, aryl-lower alkyl or hydroxy-lower alkyl.

13. Compounds according to any one of claims 1 to 12, wherein R^8 represents hydroxy-lower alkyl, carboxy-lower alkyl or aryl-lower alkyl.

14. Compounds according to any one of claims 1 to 13, wherein R^9 represents lower alkylcarbonyl or carboxy-lower alkylcarbonyl.

15. A compound according to claim 1 selected from:

2(S)-[[N-[N-[N-[N-[N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4-difluorovaleraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(methylthio)propionaldehyde;

2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(butylthio)propionaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentenaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentynal;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-

leucyl]amino]-4-hexynal;

3-(benzylthio)-2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propionaldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(2-thienyl)propionaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(3-thienyl)propionaldehyde; and

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-3-(2-naphthyl)-D-alanyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde.

16. A compound according to claim 1, selected from:

2(RS)-[[N-[N-[N-[N-[N-(3-Carboxypropionyl)-L-seryl-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]-amino]-4,4,4-trifluorobutyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]hexanal;

(Z)-2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-hexenal;

2(RS)-[[N-[N-[N-[N-[N-(benzyloxycarbonyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-4-chloro-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-methylhexanal;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-

α-glutamyl]-2-m thyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-hexenal;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-norleucyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-2-cyclohexylglycyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde; and

2(RS)-[[N-[N-[N-[N-[N-(4-acetamidobenzoyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

17. A compound according to claim 1, selected from:

1(RS)-[[N-[N-[N-[N-N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid;

1(RS)-[[N-[N-[N-[N-N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butylboronic acid; and

1(RS)-[[N-[N-[N-[N-N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-butenylboronic acid.

18. A compound according to claim 1, selected from:

1(RS)-[[N-[N-[N-[N-[N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-butenylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanyl]amino]-3-butenylboronic acid;

1(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]pentylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucyl]amino]propylboronic acid;

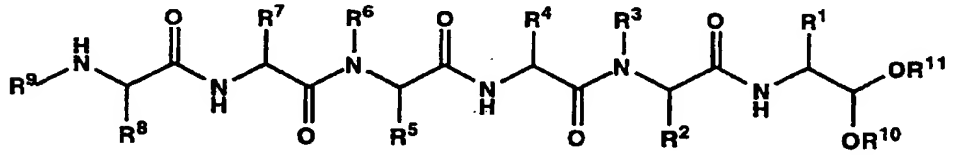
1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-L-2-cyclohexylglycyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid; and

1(RS)-[[N-[N-[N-[N-[N-(benzyloxycarbonyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl-L-leucyl]-amino]propylboronic acid.

19. A compound according to any one of claims 1 to 18 for use as a therapeutically active substance, especially as an antiviral agent and particularly as an agent against Hepatitis C, Hepatitis G or human GB viruses.

20. A process for the manufacture of a compound according to any one of claims 1 to 18 and of salts of those compounds which are acidic with bases which process comprises

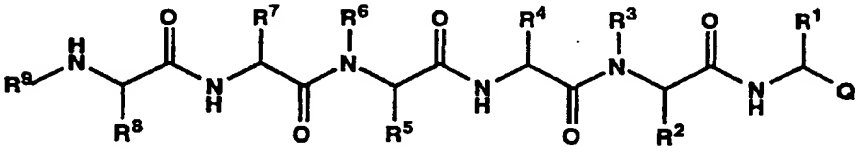
a) for the manufacture of a compound of formula I in which E represents CHO, deacetalizing and, where required, deprotecting an acetal of the general formula



(II)

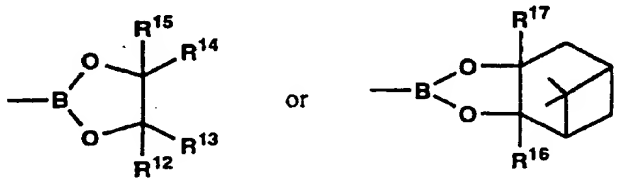
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 have the significance given in claim 1, provided that any carboxy, hydroxy and/or aminocarbonyl group(s) present is/are in protected form, and R^{10} and R^{11} each represent lower alkyl,

b) for the manufacture of a compound of formula I in which E represents $B(OH)_2$, ring opening and, where required, deprotecting a substituted dioxaborolane of the general formula



(III)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 hav the significance given in claim 1, provided that any carboxy, hydroxy and/or aminocarbonyl group(s) present may be in protected form, and Q represents a group of the formula



(a) or (b)

wherein R^{12}, R^{13}, R^{14} and R^{15} each represent hydrogen or lower alkyl and R^{16} and R^{17} each represent hydrogen or lower alkyl,

and

c) if desired, converting an acidic compound of formula I obtained into a salt with a base.

21. A process according to claim 20, wherein the acetal of formula II or substituted dioxaborolane of formula III in which Q represents a group of formula (a) is bonded to a solid phase peptide synthesis resin.

22. Acetals of formula II given in claim 20.

23. Substituted dioxaborolanes of formula III given in claim 20.

24. A medicament, especially an antiviral medicament, particularly a medicament against Hepatitis C, Hepatitis G or human GB viruses, containing a compound according to any one of claims 1 to 18 in association with a compatible pharmaceutical carrier.

25. The use of a compound according to any one of claims 1 to 18 for the production of an antiviral m dicament, especially a medicament against Hepatitis C, Hepatitis G or human GB viruses.

26. The invention as hereinbefore described.

* * *